SHORT COMMUNICATION

# Time from symptom onset to final diagnosis of pulmonary arterial hypertension in Polish patients

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**Introduction** Pulmonary arterial hypertension (PAH) is a severe, progressive disease with poor prognosis.[1-3] Early recognition of symptoms and prompt diagnosis facilitate introduction of PAH-specific treatment at earlier stages of the disease, which results in better prognosis.[4-7]

According to the Polish registry of pulmonary hypertension (PH), as many as 5.2 new cases of PAH patients per million adults are diagnosed every year,[8,9] and the mean (SD) time from the onset of symptoms to the first medical contact (FMC) is estimated at 9.6 (27.3) months. Still, the diagnostic pathway of the patient from the time of first symptoms to the time of FMC and the time of the final diagnosis at the reference center remains unknown. Therefore, we aimed to characterize the critical steps in the diagnostic process of PAH and to determine potential causes of delay in PAH diagnosis in a sample of Polish patients with PAH.

**Methods** We enrolled consecutive patients with PAH[10] who underwent routine assessment in a PH referral center for adults between March 1, 2019 and May 1, 2019 and agreed to participate in the study. We excluded patients with PAH resulting from congenital heart diseases, as they usually had their diagnosis established in childhood. We performed a prespecified interview with each patient. Data were presented as the number (percentage) or median (interquartile range [IQR]). A detailed description of the study methods is presented in Supplementary material. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was obtained from each study participant.

**Results and discussion** We enrolled 50 patients with PAH (n = 31; 62% women) at the median (IQR) age of 57 (45.5–71) years, with idiopathic PAH (n = 40 [80%]) and PAH associated with connective tissue disease (n = 10 [20%]). At the time of enrollment, most patients (n = 45 [90%]) had been previously diagnosed and 5 (10%) patients were newly diagnosed.

At enrollment, half of the patients presented with the World Health Organization functional class (WHO-FC) III (n = 25 [50%]) followed by WHO-FC II (n = 22 [44%]), IV (n = 2 [4%]), and I (n = 1 [2%]). Our study protocol and main findings are presented in FIGURE 1.

The most common first symptoms of PAH included dyspnea (n = 38 [76%]), tiredness (n = 37 [74%]), and fatigue (n = 35 [70%]). Other initial manifestations reported by patients are listed in Supplementary material, *Figure S1*. The median (IQR) number of symptoms reported by each patient was 3 (2–5).

More than half of the respondents (n = 26 [52%]) reported that their first symptoms were mild (WHO-FC II). The others reported symptoms typical of WHO-FC I (n = 5 [10%]), III (n = 17 [34%]), and IV (n = 2 [4%]).

Most patients reported their first symptoms to general practitioners (GPs; n = 25 [50%]), followed by cardiologists (n = 8 [16%]), or other specialists (n = 4 [8%]) including: 1 pulmonologist, 1 rheumatologist, and 2 physicians without specialization;

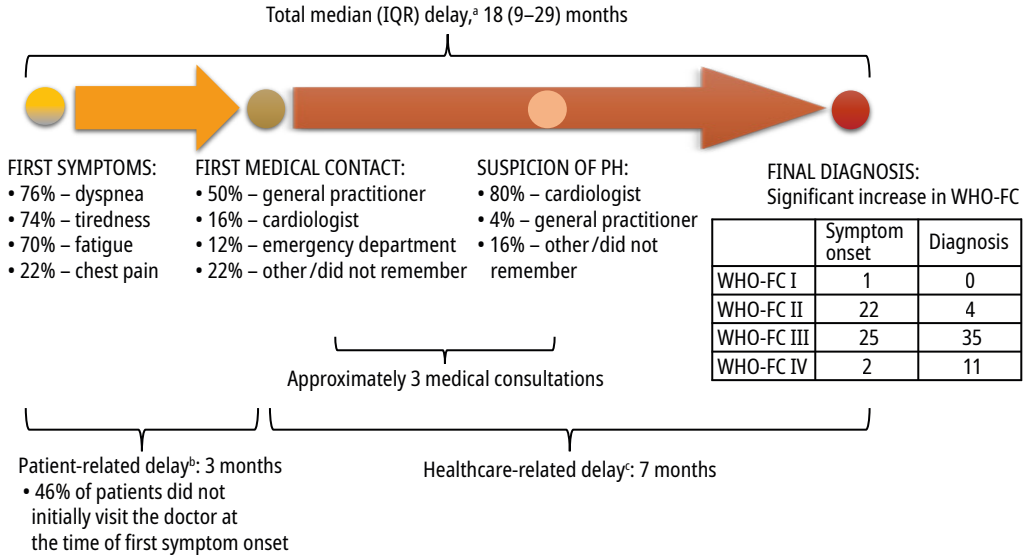


**FIGURE 1** A flowchart depicting the diagnostic pathway of patients with pulmonary arterial hypertension

**a** Total delay is the time from the onset of first symptoms to definitive PAH diagnosis.

**b** Patient-related delay is the time from the onset of first symptoms to the first medical contact.

**c** Healthcare-related delay is the time from first medical contact to definitive PAH diagnosis.

Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; IQR, interquartile range; WHO-FC, World Health Organization functional class

6 patients (12%) presented to the emergency department because of progressing exertional dyspnea; 7 patients (14%) could not provide this information. At the time of FMC, half of the patients (n = 25 [50%]) were in WHO-FC III, 8 (16%) in WHO-FC IV, 3 (6%) in WHO-FC II, and a single patient (2%) was in WHO-FC I. Thirteen patients (26%) were unable to describe the severity of symptoms at that point.

The median (IQR) time between the first manifestation(s) and FMC (patient-related delay) was 3 (1–12) months. Almost half of the patients (n = 23 [46%]) did not initially (within a week) visit the doctor when the first symptoms appeared. The most commonly indicated reasons for patient-related delay were only slight limitation of physical activity (n = 19 [38%]), expected remission of symptoms (n = 15 [30%]), and ascribing the symptoms to other disorders (n = 6 [12%]).

Conditions that prompted patients to visit a physician were disease progression (n = 20 [40%]), persistence (n = 10 [20%]), and occurrence of new symptoms (n = 9 [18%]). In the regression model including patient-related delay as a dependent variable and the number of initial symptoms, age, urban versus rural residence, education level, and number of comorbidities as independent variables, only the number of initial symptoms ($\beta = -2.84$; $r = -0.38$; $P = 0.01$) predicted the time from symptom onset to FMC.

The median (IQR) time of healthcare-related delay (the time from FMC to PAH diagnosis) was 7 (4–17) months. Before getting the initial diagnosis of PH, patients underwent a median (IQR) number of 3 (2–4) medical consultations. The initial diagnosis was made most frequently by cardiologists (n = 40 [80%]). The median (IQR) time between the initial and final diagnosis established in the PH reference center was 2.5 (1–4) months.

At the time of the initial diagnosis of PH, a half of the study patients (n = 25 [50%]) manifested exertional dyspnea at WHO-FC III, 14 (28%) at WHO-FC IV, and 8 (16%) at WHO-FC II. Three patients (6%) could not provide this information.

The median (IQR) time between first symptoms and the final diagnosis of PAH was 18 (9–29) months. During that time, patients reported progression of dyspnea from WHO-FC I/II (n = 31 [52%]) to WHO-FC III/IV (n = 46 [92%]; $P < 0.001$).

We showed that the median time between first symptoms and the final diagnosis of PAH was 18 months. Consequently, at PAH diagnosis, most patients presented with severe symptoms. The diagnostic delay was related to both patient- and healthcare-dependent factors.

Pulmonary arterial hypertension is a severe disease with very short survival in its natural history of approximately 2.8 years.[11] Therefore, of importance are the results of our study, which quantify the diagnostic delay in Polish patients with PAH and provide insight into the causes underlying this finding. The median time from the onset of symptoms to PAH diagnosis is comparable to that presented in some American reports[5,12] and shorter than observed in other studies from France (2.3 years), Germany (2.3 years),

and Australia (3.9 years).[13-15] These studies were, however, performed, on average, a decade ago and it is possible that awareness of PH was lower at that time.

The time to the final diagnosis in our study was longer than that recently presented by the authors of the Polish registry of PAH (BNP-PL); however, only incident patients were analyzed in that registry.[8]

On their way to the final diagnosis of PAH, our patients underwent a median number of 3 medical consultations which did not result in the proper diagnosis. In an Australian study, patients reported a mean number of 5.3 GP visits and 3 specialist visits,[13] whereas 54% of the patients underwent at least 3 medical consultations according to a German study.[14] These data suggest that there is insufficient awareness of PAH among GPs and specialists.

In our study, no single symptom was associated with a shorter pathway to PAH diagnosis. This was also highlighted in other studies and ascribed to a nonspecific nature of PAH symptoms resulting in their misinterpretation. We found that only the number of symptoms correlated with the time to the final diagnosis.

We concluded that the time to the final diagnosis is significantly prolonged in Polish patients with PAH owing to both patient- and healthcare--related factors. Therefore, further effort is needed to build PAH awareness at the society and healthcare level.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

## ARTICLE INFORMATION

**CONFLICT OF INTEREST** None declared.



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## REFERENCES

1 Vachiery JL, Coghlan G. Screening for pulmonary arterial hypertension in systemic sclerosis. Eur Respir Rev. 2009; 18: 162-169.

2 Jonas K, Kopeć G. HDL cholesterol as a marker of disease severity and prognosis in patients with pulmonary arterial hypertension. Int J Mol Sci. 2019; 20: 3514.

3 Jonas K, Kopeć G. A challenging phenotype of pulmonary arterial hypertension. Pol Arch Intern Med. 2020; 130: 85-86.

4 Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation. 2010; 122: 156-163.

5 Brown LM, Chen H, Halpern S, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. Chest. 2011; 140: 19-26.

6 McLaughlin, V, Shillington A, Rich S. Survival in primary pulmonary hypertension. Circulation. 2002; 106: 1477-1482.

7 Kopeć G, Waligóra M, Jonas K, et al. Epoprostenol therapy for pulmonary arterial hypertension: the first Polish experience. Pol Arch Intern Med. 2019; 129: 65-68.

8 Kopeć G, Kurzyna M, Mroczek E, et al. Characterization of patients with pulmonary arterial hypertension: data from the Polish Registry of Pulmonary Hypertension (BNP-PL). J Clin Med. 2020; 9: 173.

9 Kopeć G, Kurzyna M, Mroczek E, et al. Database of Pulmonary Hypertension in the Polish Population (BNP-PL): design of the registry. Kardiol Pol. 2019; 77: 972-974.

10 Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2016; 37: 67-119.

11 D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991; 115: 343-349.

12 Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med. 1987; 107: 216-223.

13 Strange G, Gabbay E, Kermeen F, et al. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: the delay study. Pulm Circ 2013; 3: 89-94.

14 Wilkens H, Grimminger F, Hoeper M, et al. Burden of pulmonary arterial hypertension in Germany. Respir Med. 2010; 104: 902-910.

15 Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: Results from a national registry. Am J Respir Crit Care Med 2006; 173: 1023-1030.